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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/217,324	03/24/94	OSBORNE	W...163363

EXAMINER

MILNE, A

ART UNIT	PAPER NUMBER
1804	15

DATE MAILED: 05/12/97

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 2-11-97

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-22 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-22 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Claims 1-22 are currently pending in U.S. Patent Application Number 08/217,324. The response filed 2-11-97 (paper #14) has been entered and carefully reviewed.

The rejection based upon the first paragraph of 35 U.S.C. § 112 is hereby considered withdrawn, as it relates to claims 1-10, in light of the response filed 2-11-97 (paper #14).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

Applicants argue that the rejection of record fails to provide specific and sufficient evidence supporting the opinion that the claims are not enabled by the specification. The response indicates that a somewhat blanket rejection has been made with no specific arguments which indicate why the claimed invention is not enabled.

More specifically, applicants argue on page 10 of the response:

> "In summary, the Examiner has provided no evidence that the use of different vector systems to transduce smooth muscle cells to express different genes of interest within Applicants' invention would require undue experimentation. As previously noted, Applicants' invention does not rely on the particular vectors and genes chosen to implement the invention, but in the proven devices and methods for engrafting transduced vascular smooth muscle cells into a mammalian subject to deliver useful proteins. Choice of vectors and genes to achieve successful adaptation of these devices and methods, based on Applicants teachings' and general knowledge in the art at the time of the invention, would require no more than routine manipulation and optimization of known parameters." [underscore added]

These arguments are not deemed persuasive. The two previous office actions clearly addressed the high level of unpredictability in the art of gene therapy. The fact that no narrow and specific reference has been offered to profess the high level of unpredictability in the art with regards to applicants specific invention does not take away from the fact that the level of unpredictability in the art at the time the invention was made was such that undue experimentation be required to practice the claimed invention. It is well known in

the art that while some progress has been made toward human gene therapy, only a handful of clinical trials and very limited success have been reported to date. It is noted that the **unpredictability** of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of a claim. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). With respect to a prima facie case of nonenablement, while a single embodiment may provide broad enablement in cases involving predictable factors, in cases involving unpredictable factors, such as physiological activity, a further showing is required. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Claims 11-22 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

1. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

Claims 1-22 stand rejected under 35 U.S.C. § 103 as being unpatentable over Zalewski et al. (WO 93/15609) taken with Nabel et al. (U.S. 5,328,470) and Anderson et al. (WO 90/224,525).

Applicants argue that the Zalewski et al. reference fails to adequately suggest the claimed invention as it relates only to injection and catheter-based implant devices. For example, page 32 of the response states:

> "On the contrary, the devices and methods taught by Zalewski et al. are entirely inapposite to Applicants' claimed devices and methods for implanting vascular grafts seeded with autologous transduced smooth muscle cells. The Zalewski et al. reference only teaches "injection and transcatheter delivery devices to deliver a solution" or a "perfusate" under pressure, containing only genes and vectors to transform smooth muscle cells in situ (see e.g. page 8, lines 21-23; page 9, lines 14-35, page 10, lines 4-8). The use of these devices is transitory, i.e. lasting 1-2 minutes, based on the requirement for occlusion of the target vessel and concomitant risk of myocardial infarction (see, e.g. page 10, lines 21-23; page 9, lines 14-35, page 10, lines 4-8). There is absolutely no disclosure or suggestion of devices or methods "to hold and contain" transduced smooth muscle cells, particularly in the manner of Applicants' prosthetic devices which are seeded with cells and implanted as a long term graft."

These arguments are not deemed persuasive as the rejection in the previous action was made as a result of properly combining the prior art to arrive at applicants' invention with both motivation to do so and a substantial expectation of success. The fact that the Zalewski et al. reference does not specifically disclose an implantable prosthetic device lined with SMC (smooth muscle cells) does not take away from the fact that the Nabel reference does. Moreover, Anderson et al. also discloses to the skilled artisan a vascular graft coated with genetically modified autologous endothelial cells , and further discloses the use of this invention to deliver erythropoietin, Factor IX, G-CSF and GM-CSF proteins, among others.

The Nabel reference discloses the in situ transduction of endothelial and smooth muscle cells of the artreial wall or the deposition of cells transduced *ex vivo*, using the catheter to deposit the cells or appropriate gene transfer vehicle (pages 68, see "II: Introduction of cells expressing normal or exogenous proteins into the vasculature "). Nabel discloses the use of the invention to deliver insulin (page 5, line 30), or anticoagulant factors such as urokinase (page 11, lines 46-49). Nabel thus discloses in situ gene transduction of smooth muscle cells for therapeutic benefit, but does not disclose a vascular graft containing transduced smooth muscle cells as the method of delivering the gene product of interest.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a synthetic vascular graft to transplant endothelial and smooth muscle cells into a blood vessel and to substitute genetically modified cells for unmodified cells, based on the teachings of the Nabel reference to genetically modify cells of the arterial wall for therapeutic purposes. Therefore, absent any unexpected results, the invention is considered *prima facie* obvious over the prior art of record. In order to establish unexpected results for a claimed invention, the objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980); In re Greenfield, 571 F.2d 1185, 197 USPQ 227 (CCPA 1978); In re Tiffin, 443 F.2d 394, 170 USPQ 88 (CCPA 1971).

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE

MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne
AM
5-7-97

Jasemine C. Chambers
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